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Extreme Hypertriglyceridemia Revealing Clinically Suspected Congenital Generalized Lipodystrophy in Adulthood : A Diagnosic Challenge

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Abstract:
Lipodystrophy syndromes are rare disorders characterized by a deficiency of adipose tissue and associated severe metabolic complications. We report the case of a 41-year-old woman with long-standing diabetes diagnosed at the age of 16, following diabetic ketoacidosis and recurrent metabolic decompensations, and a prior episode of acute pancreatitis.
On physical examination, she exhibited marked generalized lipoatrophy with a body mass index of 13.4 kg/m². Laboratory investigations revealed extreme hypertriglyceridemia (150 g/L), predominantly composed of very-low-density lipoproteins, along with poor glycemic control (HbA1c 12%).
The association of early-onset diabetes, severe lipoatrophy, hepatic steatosis, and marked hypertriglyceridemia was strongly suggestive of congenital generalized lipodystrophy based on clinical and metabolic features, although genetic testing was unavailable due to financial constraints.
Management included strict lipid restriction, optimization of insulin therapy, fenofibrate, omega-3 supplementation, and a short period of fasting, resulting in a reduction of triglyceride levels from 150 g/L to 0.56 g/L.
Despite longstanding diabetes and a single episode of severe acute pancreatitis (Balthazar grade E) in 2015, the diagnosis was not made until adulthood. This case shows why lipodystrophy deserves consideration whenever hypertriglyceridemia reaches extreme levels, since earlier suspicion could help avoid pancreatitis and improve long-term metabolic outcomes.

Keywords: Congenital generalized lipodystrophy; severe hypertriglyceridemia; acute pancreatitis

Introduction:

Lipodystrophy syndromes are rare and clinically heterogeneous, and for that reason are often missed, defined by a partial or generalized lack of adipose tissue. Rare as they are, these conditions offer a useful model for understanding just how central fat tissue is to normal metabolic regulation.

When adipose tissue cannot store fat properly, triglycerides end up deposited in the liver and skeletal muscle instead. This ectopic fat accumulation drives insulin resistance, diabetes mellitus, hepatic steatosis, and severe dyslipidemia (1,2). It makes an interesting counterpoint to metabolic syndrome: there, it is excess fat tissue that causes these complications, whereas in lipodystrophy the near-total absence of fat tissue produces an equally severe metabolic picture (1).

Congenital generalized lipodystrophy (CGL), also known as Berardinelli–Seip syndrome, is an autosomal recessive disorder so rare that few clinicians will ever encounter it. It usually appears from birth or early infancy and is most often linked to mutations in AGPAT2 or BSCL2, genes involved in adipocyte differentiation and lipid metabolism (2,3). Affected patients typically have almost no subcutaneous fat, a muscular build, hepatomegaly from steatosis, and early metabolic complications, chiefly severe insulin resistance and hypertriglyceridemia (2,4).

Much of this metabolic picture comes down to two things: the inability to store lipids properly, and a deficiency in adipokines, leptin above all. Low leptin drives increased appetite, worsens hepatic steatosis, and deepens insulin resistance, compounding an already difficult metabolic situation (2,6,10).

Of these complications, hypertriglyceridemia is the one that worries clinicians most, since it can reach extreme levels and carries a real risk of acute pancreatitis. Recognizing it early matters, because dietary measures, lipid-lowering drugs, and, in some cases, leptin replacement can meaningfully change the outcome (4–6). Here we describe a case of exceptionally severe endogenous hypertriglyceridemia in a woman with marked lipoatrophy, whose congenital generalized lipodystrophy was suspected only in adulthood and could not be confirmed genetically. Both how high her triglycerides climbed and how long the diagnosis took to reach illustrate just how easily this condition can be missed.

This report aims to draw attention to lipodystrophy as a diagnosis worth considering in patients with extreme hypertriglyceridemia and unusual fat distribution, and to discuss what this means for diagnosis and treatment

Case Presentation :

A 41-year-old woman was diagnosed with diabetes mellitus at the age of 16 years following an episode of diabetic ketoacidosis and had since been managed with a basal–bolus insulin regimen. During follow-up, she experienced two additional episodes of diabetic ketoacidosis, both likely precipitated by urinary tract infections.

Her family history was significant for type 2 diabetes mellitus in first-degree relatives, whereas lipodystrophy, familial dyslipidemia, and other inherited metabolic disorders were not reported. Data on parental consanguinity could not be obtained.

The patient had a history of chronic hepatic steatosis, first identified on abdominal imaging at the age of 30 years and subsequently confirmed on repeated evaluations. At the age of 39 years, she developed an episode of acute pancreatitis of uncertain etiology (1).

At presentation, she was hemodynamically and respiratorily stable. Her weight was 34 kg, height 1.59 m, and body mass index 13.4 kg/m², indicating severe underweight status.

Physical examination revealed a near-complete absence of subcutaneous adipose tissue affecting the face, trunk, and extremities, resulting in a striking generalized lipoatrophic phenotype. Marked muscular prominence with visible superficial veins and pronounced bony landmarks, particularly over the clavicles and limbs, were observed. No acromegaloid appearance, facial dysmorphism, clitoromegaly, or

umbilical abnormalities were noted. There was no evidence of eruptive xanthomas or acanthosis nigricans. Diffuse cutaneous xerosis was present (Figure 1).

Abdominal examination did not reveal clinically detectable hepatomegaly; however, abdominal ultrasound demonstrated hepatic steatosis, characterized by diffusely increased liver echogenicity, in the absence of associated hepatomegaly. The combination of generalized lipoatrophy, apparent muscular hypertrophy, prominent superficial veins, severe hypertriglyceridemia, hepatic steatosis, and early-onset diabetes strongly supported the clinical suspicion of congenital generalized lipodystrophy.

Table 1: Chronological timeline of clinical events

Age	Clinical event
16 years	Diabetes mellitus diagnosed following diabetic ketoacidosis
16–41 years	Basal–bolus insulin therapy
Adulthood	Two recurrent episodes of diabetic ketoacidosis
30 years	Hepatic steatosis identified on abdominal imaging
39 years	Acute pancreatitis
41 years	Extreme hypertriglyceridemia (150 g/L) leading to investigation and clinical suspicion of congenital generalized lipodystrophy

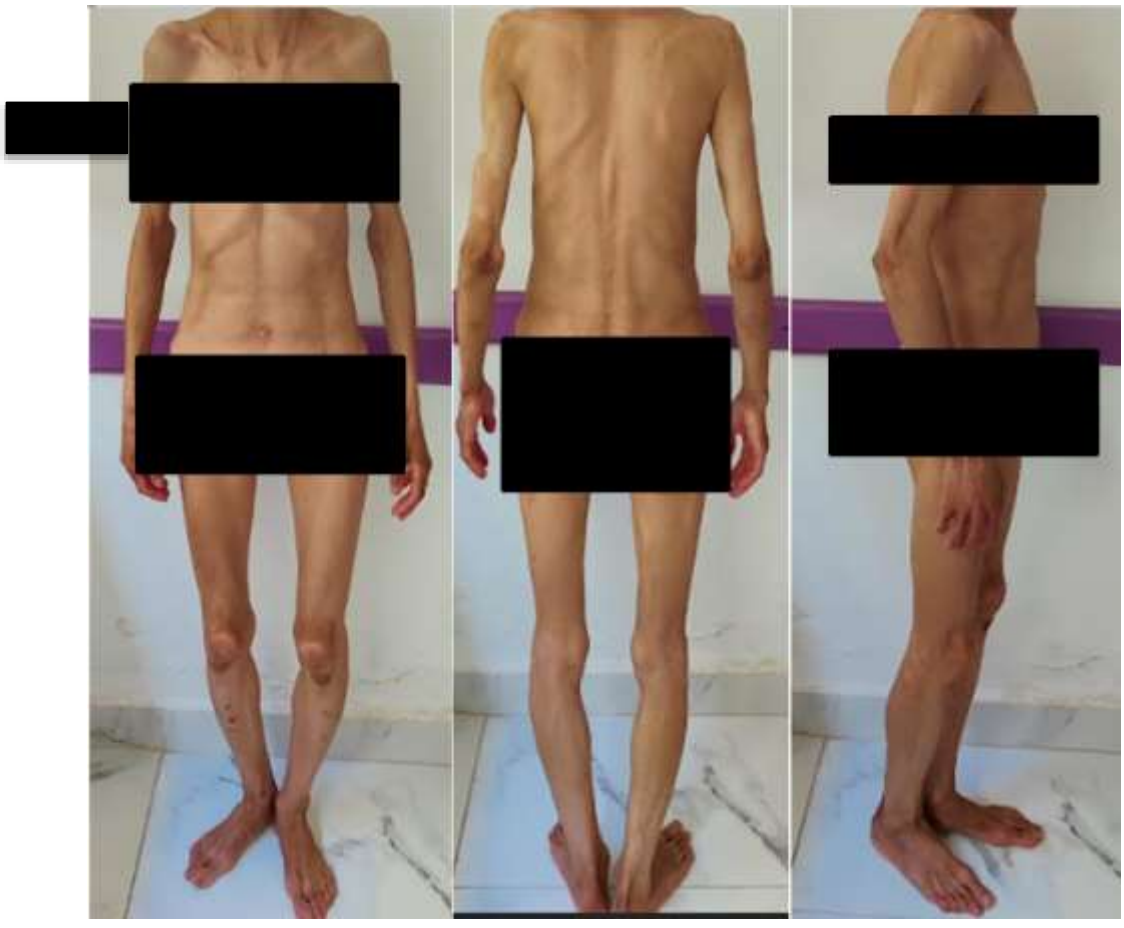

Figure 1: Clinical photograph demonstrating severe generalized lipoatrophy with prominent bony structures and near-complete absence of subcutaneous adipose tissue.

Initial laboratory tests revealed extreme hypertriglyceridemia (150 g/L), with a lactescent serum appearance suggestive of severe hypertriglyceridemia or mixed hyperlipidemia. The complete lipid profile showed markedly elevated total cholesterol (15.17 g/L) and severely reduced HDL cholesterol (0.05 g/L), consistent with a profound quantitative and qualitative lipid disturbance. Following institution of a fat-free (water-only) diet, triglyceride levels decreased but remained markedly elevated at 104 g/L, total cholesterol decreased to 12.66 g/L, while HDL cholesterol showed only partial improvement (0.18 g/L). Further etiological investigations were subsequently performed.

The creaming test, performed after 12 hours at 4°C, was negative, with no visible creamy supernatant and a turbid infranatant. These findings were consistent with a predominance of very-low-density lipoproteins (VLDL) rather than chylomicrons (Figure 2).

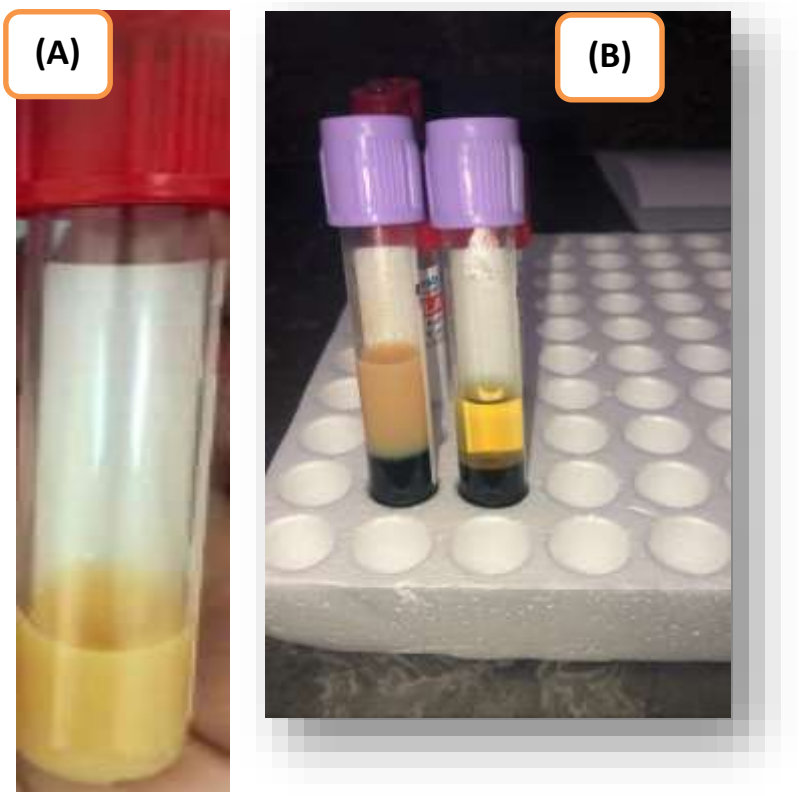

Figure 2: Lipemic serum and creaming test findings.

(A): Lactescent serum observed before refrigeration, indicating severe hypertriglyceridemia. **(B)**: Creaming test performed after 12 hours of refrigeration at 4 °C showing the absence of a creamy supernatant and the persistence of a turbid infranatant. This pattern indicates a predominance of very-low-density lipoproteins (VLDL) rather than chylomicrons.

Lipoprotein electrophoresis demonstrated clear serum with absence of chylomicrons and the following distribution (table 1).

Lipoprotein	Percentage (%)
HDL	0.6
VLDL	95.1
LDL	4.3
Chylomicrons	Absent

Table 1: Lipoprotein distribution (%) on lipoprotein electrophoresis.

Apolipoprotein A and B levels were not measured. Decantation after 24 hours at 4°C was negative, further supporting the electrophoresis findings. Glycemic control was markedly impaired, with an HbA1c of 12%. Thyroid function tests, autoimmune screening, and renal parameters were within normal limits, arguing against hypothyroidism, autoimmune-related acquired lipodystrophy, and nephrotic syndrome as secondary causes of the metabolic disturbances. There was no history of HIV infection, antiretroviral or other lipodystrophy-inducing drug exposure, alcohol use, or corticosteroid therapy that could account for an acquired form of lipodystrophy or secondary hypertriglyceridemia. Additional metabolic investigations, including serum leptin, insulin levels, and C-peptide, were not available due to limited resources.

Taken together, the early onset and generalized distribution of lipoatrophy, together with the exclusion of the main acquired and secondary causes of lipodystrophy and hypertriglyceridemia, combined with early-onset diabetes, recurrent extreme hypertriglyceridemia, and hepatic steatosis, raised a strong clinical suspicion of a congenital lipodystrophy syndrome, most likely congenital generalized lipodystrophy. Genetic testing was recommended but could not be performed due to financial constraints.

Management consisted of a strict lipid-restricted diet, optimization of insulin therapy, and pharmacological treatment including fenofibrate, omega-3 fatty acids (500 mg twice daily), and rosuvastatin (20 mg once daily). A short 72-hour fasting period was also implemented. This combined approach resulted in a rapid and favorable biochemical response, with triglyceride levels progressively decreasing from 150 g/L to 104 g/L, 43.2 g/L, and ultimately reaching near-normal levels of 0.56 g/L.

Discussion :

Congenital generalized lipodystrophy (CGL) is difficult to diagnose and, once diagnosed, difficult to manage. What makes our patient unusual is the combination of extreme hypertriglyceridemia (150 g/L), long-standing diabetes, hepatic steatosis, and a diagnosis that took more than two decades to reach: most reported cases of CGL are identified in early infancy or childhood, not in a 41-year-old woman (5,6,11).

The lipid abnormalities in our patient fit the known pathophysiology of generalized lipodystrophy reasonably well. Without functional adipose tissue to store triglycerides, lipids accumulate ectopically in the liver and skeletal muscle, driving insulin resistance, hepatic steatosis, and excess hepatic production of VLDL (2,3,6,11). Her lipoprotein electrophoresis, in which VLDL accounted for 95.1% of circulating lipoproteins, fits this pattern of endogenous overproduction. Adipokine deficiency, particularly of leptin, likely played a role as well: low leptin drives hyperphagia, insulin resistance, hepatic steatosis, and severe hypertriglyceridemia (6,8,11). We could not measure her leptin level, but given how severe her metabolic phenotype was, this mechanism was probably involved, as it appears to be in comparable published cases.

Clinically, she had generalized lipoatrophy of the face, trunk, and limbs, prominent musculature, visible superficial veins, early-onset diabetes, severe hypertriglyceridemia, chronic hepatic steatosis, and a history of pancreatitis, a constellation that, per current recommendations, should prompt consideration of a generalized lipodystrophy syndrome (5,6,11). What stands out most is how long this went unrecognized. She was diagnosed with diabetes at 16, had two further episodes of ketoacidosis, developed chronic hepatic steatosis, and had a bout of acute pancreatitis, and still the underlying disorder was not identified until adulthood. This is a fairly common pattern with lipodystrophy: attention

goes to the metabolic complications, and the body fat distribution goes unexamined. A careful look at a patient's build can be revealing even without access to specialized testing. The ketoacidosis is worth a closer look too. Diabetes in CGL usually reflects severe insulin resistance rather than true insulin deficiency, so ketoacidosis is not the expected presentation. Here, the first ketoacidotic episode likely led to an initial diagnosis of type 1 diabetes, which may partly explain why the lipodystrophy was missed for so long, a reminder that CGL does not always follow the textbook course.

On the laboratory side, the triglyceride level itself stands out: 150 g/L is exceptionally high, even against other published CGL cases, and put her at real risk of acute pancreatitis, which is almost certainly what happened to her in 2015. Lipoprotein electrophoresis and a negative refrigeration test both pointed to endogenous VLDL overproduction rather than defective chylomicron clearance. Our workup had real limits: we could not obtain genetic confirmation for financial reasons, and leptin, insulin, C-peptide, and apolipoprotein levels were all unavailable. Imaging was limited to abdominal ultrasound, so we could not map her adipose tissue distribution the way whole-body MRI or DEXA would in a better-resourced setting.

We also had to rule out several alternative diagnoses. Severe malnutrition, cachexia, and anorexia nervosa can all cause marked fat loss and a low BMI, but none of them explain diabetes, hepatic steatosis, and severe hypertriglyceridemia occurring together. HIV-associated lipodystrophy was unlikely given the absence of any history of HIV infection or antiretroviral exposure. We considered acquired generalized lipodystrophy, but the early onset and the long clinical course pointed toward a congenital cause instead. Familial chylomicronemia syndrome was excluded by the absence of chylomicrons on electrophoresis and a negative refrigeration test, both consistent with a VLDL-driven rather than chylomicron-driven process.

Treatment consisted of strict dietary fat restriction, optimized insulin therapy, fenofibrate, omega-3 fatty acids, rosuvastatin, and a brief fasting period, and her triglycerides fell sharply to 0.56 g/L. That kind of response points to hepatic substrate overload and VLDL overproduction as the main drivers of her hypertriglyceridemia, in keeping with what has been reported in similar cases. Metreleptin is now considered the mainstay of treatment for generalized lipodystrophy with leptin deficiency, with reported benefits for glycemic control, triglycerides, hepatic steatosis, and overall metabolic status (7–12). We had access to neither leptin testing nor metreleptin, which reflects the resource constraints of our setting more than anything about the patient herself. Still, taken as a whole, the lipoatrophy, the early-onset diabetes, the hepatic steatosis, the pancreatitis, and the VLDL-driven hypertriglyceridemia make a strong case for congenital generalized lipodystrophy, genetic testing or not.

Conclusion :

Extreme hypertriglyceridemia in a patient with severe generalized lipoatrophy should raise the possibility of congenital generalized lipodystrophy, even in an adult with no prior suspicion of the condition.

In our patient, the phenotype went unrecognized for more than twenty years despite early-onset diabetes, hepatic steatosis, and pancreatitis, and her triglyceride level is among the highest reported in an adult with this condition.

We could not confirm the diagnosis genetically, but the clinical and metabolic picture was convincing enough on its own, which speaks to the value of a careful look at body fat distribution when genetic

testing is out of reach. Recognizing this disorder early matters because it can help prevent complications such as pancreatitis and allow for timely, targeted treatment, metreleptin included where available.

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